WHAT IS CLAIMED IS:

1. A method of identifying a second oligopeptide to which a first oligopeptide binds, said method comprising:

contacting said first oligopeptide to said second oligopeptide, wherein said first and said second oligopeptides are translated from a nucleic acid encoding a fusion protein comprised of a circularly permutated marker protein fused in frame through a first break-point terminus and a second break-point terminus to said first oligopeptide and said second oligopeptide, respectively, wherein association of said first oligopeptide to said second oligopeptide results in functional reassembly of said circularly permutated marker protein to produce a directly detectable signal;

isolating nucleic acids encoding fusion proteins that produce said directly detectable signal; and

identifying the nucleic acid sequence encoding said second oligopeptide that binds to said first oligopeptide, whereby said second oligopeptide to which said first oligopeptide binds is identified.

2. The method according to Claim 1, wherein contacting of said first oligopeptide to said second oligopeptide is carried out *in vitro* in a host cell lysate.

3. The method according to Claim 1, wherein said fusion protein is expressed in a host cell.

4. The method according to Claim 3, wherein said fusion protein further comprises an N-terminal signal peptide.

5. The method according to Claim 4, wherein said host cell is a bacterial cell.

6. The method according to Claim 5, wherein said signal peptide provides for translocation to the periplasm of said bacterial cell.

7. The method according to Claim 6, wherein said bacterial cell is an *E. coli* cell.

8. The method according to Claim 5, wherein said association of said first oligopeptide to said second oligopeptide provides for an activation index of from 10^3 to 10^7.

9. The method according to Claim 3, wherein said host cell is a eukaryotic cell.

10. The method according to Claim 9, wherein said first oligopeptide is a phosphorylation-regulated signal transducer protein.

11. The method according to Claim 10, wherein said phosphorylation-regulated signal transducer protein is a tyrosine kinase.

12. The method according to Claim 1, wherein said marker protein is a monomeric enzyme.

13. The method according to Claim 12, wherein said enzyme provides for antibiotic resistance.

14. The method according to Claim 13, wherein said enzyme that provides for antibiotic resistance is a β-lactamase.

15. A method of identifying a second oligopeptide to which a first oligopeptide binds, said method comprising:

expressing in a host cell a nucleic acid encoding a fusion protein comprised of a circularly permutated marker protein fused in frame through a first break-point terminus and a second break-point terminus to said first oligopeptide and said second oligopeptide, respectively, wherein at least one of said first oligopeptide and said second oligopeptide is a member of a proteome library, wherein association of said first oligopeptide to said second oligopeptide results in functional reassembly of said circularly permutated marker protein to produce a directly detectable signal;

isolating host cells expressing nucleic acids encoding fusion proteins that produce said directly detectable signal; and

identifying the nucleic acid sequence encoding said second oligopeptide that binds to said first oligopeptide, whereby said second oligopeptide to which said first oligopeptide binds is identified.

16. The method according to Claim 15, wherein said fusion protein further comprises an N-terminal signal peptide.

17. The method according to Claim 16, wherein said host cell is a eukaryotic cell.

18. The method according to Claim 17, wherein said signal peptide provides for production of said directly detectable signal in a subcellular compartment selected from the group consisting of the cytoplasm, the nucleus, and the endoplasmic reticulum or in association with the extracellular membrane of said eukaryotic cell.

19. The method according to Claim 15, wherein said proteome library is selected from the group consisting of a single chain antibody Fv fragment library, an antibody light chain variable region library, and a peptide library displayed within thioredoxin.

20. The method according to Claim 15, wherein said marker protein is a β-lactamase.

21. A method of identifying a third oligopeptide to which a first oligopeptide and a second oligopeptide simultaneously bind, said method comprising:

expressing in a multiplicity of host cells a first nucleic acid sequence encoding a fusion protein comprised of a circularly permutated marker protein fused in frame through a first break-point terminus and a second break-point terminus to a first oligopeptide and a second oligopeptide, respectively, and a second nucleic acid sequence encoding a third oligopeptide, wherein simultaneous association of said first oligopeptide and said second oligopeptide to said third oligopeptide results in the functional reassembly of said circularly permutated marker protein,

isolating host cells expressing nucleic acids encoding fusion proteins that produce said directly detectable signal; and

identifying said second nucleic acid sequence encoding said third oligopeptide that binds simultaneously to said first oligopeptide and said second oligopeptide, whereby said third oligopeptide to which said first oligopeptide and said second oligopeptide binds is identified.

22. The method according to Claim 21, wherein said marker protein is a β-lactamase.

23. The method according to Claim 22, wherein said host cell is a prokaryotic cell.

24. An interaction-dependent enzyme activation system, said system comprising:
a nucleic acid sequence encoding a first oligopeptide and a second oligopeptide, each fused in frame through a first and a second break-point terminus, respectively, to a circularly permutated marker protein, wherein said circularly permutated marker protein reassembles to form a functionally reconstituted marker protein that produces a detectable signal upon the association of said first oligopeptide with said second oligopeptide or upon simultaneous association of said first oligopeptide and said second oligopeptide with a third oligopeptide.

25. The interaction-dependent enzyme activation system according to Claim 24, wherein said first oligopeptide and said second oligopeptide each further comprise a cysteine residue within 5 amino acid positions of said first and said second break-point terminus.

26. The interaction-dependent enzyme activation system according to Claim 25, wherein said cysteine residue is at said break-point terminus.

27. The interaction-dependent enzyme activation system according to Claim 25, wherein said first oligopeptide and second oligopeptide each further comprise a flexible polypeptide linker fused in frame to each of said first and said second break-point terminus.

28. The interaction-dependent enzyme activation system according to Claim 24, wherein functional reconstitution of said marker protein is enhanced by introducing at least one of the following modifications to at least one of said first and said second oligopeptide sequences:
i) a randomly-encoded peptide of 3-12 amino acids encoded between said break-point terminus and said flexible polypeptide linker,
ii) a randomly-encoded peptide of 3-12 amino acids expressed separately and operably fused to the N-terminus of a thioredoxin,
iii) a cysteine residue encoded between said oligopeptide and said flexible polypeptide linker, or
iv) 1-3 codon changes within said circularly permutated marker protein that enable more stable folding of a reconstituted marker protein.

29. The interaction-dependent enzyme activation system according to Claim 28, wherein said randomly-encoded peptide of 3-12 amino acids, is a tripeptide.

30. The interaction-dependent enzyme activation system according to Claim 29, wherein said tripeptide is selected from the group consisting of HSE, NGR, GRE, EKR, REQ, QGN, DGR, GRR and GNS.

31. The interaction-dependent enzyme activation system according to Claim 25, wherein said system provides for an activation index of between 10^3 and 10^7.

32. The interaction-dependent enzyme activation system according to Claim 24, wherein said marker protein provides for a directly detectable signal.

33. The interaction-dependent enzyme activation system according to Claim 32, wherein said directly selectable signal is a visible phenotypic change or antibiotic resistance.

34. The interaction-dependent enzyme activation system according to Claim 32, wherein said marker protein that provides for a directly selectable signal is a monomeric enzyme.

35. The interaction-dependent enzyme activation system according to Claim 34, wherein said enzyme provides for antibiotic resistance.

36. An interaction-dependent enzyme activation system, said system comprising:
a first nucleic acid sequence encoding a first oligopeptide and a second oligopeptide, each fused in frame through a first and a second break-point terminus, respectively, to a circularly permutated β-lactamase, wherein said circularly permutated β-lactamase reassembles to form a functionally reconstituted marker protein that produces a detectable signal upon the association of said first oligopeptide with said second oligopeptide or upon simultaneous association of said first oligopeptide and said second oligopeptide with a third oligopeptide encoded by a second nucleic acid sequence.

37. The interaction-dependent enzyme activation system according to Claim 36, wherein said β-lactamase is a Type A β-lactamase.

38. The interaction-dependent enzyme activation system according to Claim 37, wherein said Type A β-lactamase is a TEM-1 β-lactamase.

39. The interaction-dependent enzyme activation system according to Claim 38, wherein said β-lactamase comprises at least one mutation selected from the group consisting of K55E, P62S and M182T.

40. The interaction-dependent enzyme activation system according to Claim 38, wherein said break-point terminus of said β-lactamase is within ten residues in either direction from a junction between amino acid residues selected from the group consisting of N52/S53, Q99/N100, P174/N175, E197/L198, K215/V216, A227/G228, and G253/K254.

41. The interaction-dependent enzyme activation system according to Claim 38, wherein said break-point of said β-lactamase is within ten residues in either direction from a junction between amino acid residues E197 and L198 or amino acid residues A227 and G228.

42. The interaction-dependent enzyme activation system according to Claim 36, wherein an N-terminal segment and a C-terminal segment comprising the native β-lactamase of said circularly permutated marker protein together comprise one of a contiguous, overlapping or non-continuous sequence of said native parent protein and comprise between about 90 to 110% of the total length of said native parent protein.

43. The interaction-dependent enzyme activation system according to Claim 36, wherein said circularly permutated marker protein is expressed with an N-terminal signal peptide.

44. The interaction-dependent enzyme activation system according to Claim 43, wherein said signal peptide provides for translocation to the periplasm of a bacterial cell.

45. The interaction-dependent enzyme activation system according to Claim 44, wherein said bacterial cell is an *E. coli* cell.

46. The interaction-dependent enzyme activation system according to Claim 45, wherein said system provides for plating efficiencies between 0.01-1.0 colonies per cell.

47. The interaction-dependent enzyme activation system according to Claim 43, wherein said signal peptide provides for translocation to the extracellular membrane of a eukaryotic cell.

48. The interaction-dependent enzyme activation system according to Claim 47, wherein at least one of said first oligopeptide and said second oligopeptide is an extracellular protein.

49. The interaction-dependent enzyme activation system according to Claim 46, wherein at least one of said first oligopeptide and said second oligopeptide is a cell surface molecule.

50. The interaction-dependent enzyme activation system according to Claim 36, wherein at least one of said first oligopeptide said second oligopeptide is a member of a library.

51. The interaction-dependent enzyme activation system according to Claim 50, wherein at least one of said first oligopeptide and said second oligopeptide is a member of a library selected from the group consisting of a single chain antibody Fv fragment library, an antibody light chain variable region library, and a peptide library library displayed within thioredoxin.

52. The interaction-dependent enzyme activation system according to Claim 36, wherein said system provides for a unimolecular bipartite association.

53. The interaction-dependent enzyme activation system according to Claim 36, wherein said system provides for a bimolecular tripartite association.

54. An intracellular signal transduction biosensor, said biosensor comprising:

a first nucleic acid sequence encoding a first intracellular polypeptide and a second intracellular polypeptide, each fused in frame through a first and a second break-point terminus, respectively, to a circularly permutated β-lactamase, wherein said circularly permutated β-lactamase reassembles to form a functionally reconstituted marker protein that produces a detectable signal upon the association of said first oligopeptide with said second oligopeptide or upon simultaneous association of said first oligopeptide and said second oligopeptide with a third intracellular polypeptide encoded by a second nucleic acid sequence.

55. The intracellular signal transduction biosensor according to Claim 54, wherein said first intracellular polypeptide is a phosphorylation-regulated signal transducer protein.

56. The intracellular signal transduction biosensor according to Claim 55, wherein said phosphorylation-regulated signal transducer protein is a tyrosine kinase.

57. An expression cassette comprising:
as operably linked components in the direction of transcription nucleotide sequences encoding for:
(i) a promoter functional in a host cell;
(ii) a first polypeptide interactor domain;
(iii) a circularly permutated marker protein;
(iv) a second polypeptide interactor domain.

58. The expression cassette according to Claim 57, further comprising a second expression cassette that encodes for a third polypeptide that simultaneously binds to said first polypeptide and said second polypeptide.

59. The expression cassette according to Claim 57, further comprising nucleotide sequences encoding for a first flexible polypeptide linker situated between said first polypeptide interactor domain and said circularly permutated marker protein, and a second flexible polypeptide linker situated between said circularly permutated marker protein and said second polypeptide interactor domain.

60. The expression cassette according to Claim 57, further comprising nucleotide sequences encoding for a first cysteine residue situated between said first flexible polypeptide linker and said circularly permutated marker protein, and a second cysteine residue situated between said second flexible polypeptide linker and said circularly permutated marker protein.

61. The expression cassette according to Claim 57, further comprising a sequence encoding for a signal peptide.

62. The expression cassette according to Claim 61, wherein said a signal peptide provides for translocation to the periplasm of a bacterial cell.

63. The expression cassette according to Claim 57, wherein at least one of said first polypeptide interactor domain and said second polypeptide interactor domain is an intracellular protein.

64. The expression cassette according to Claim 57, wherein said marker protein is an enzyme.

65. The expression cassette according to Claim 62, wherein said enzyme is β-lactamase.

66. A plasmid comprising an expression cassette according to Claim 57.

67. A plasmid comprising an expression cassette according to Claim 58.

68. A host cell comprising a plasmid according to Claim 66.

69. A host cell comprising a plasmid according to Claim 67.

70. The host cell according to Claim 68, wherein said host cell is a prokaryotic cell.

71. The host cell according to Claim 69, wherein said host cell is a prokaryotic cell.

72. A DNA sequence comprising as operably linked components in the direction of transcription, nucleic acid sequences encoding a first interactor domain, a circularly permutated marker protein, and a second interactor domain, wherein said circularly permutated marker protein functionally reassembles upon binding of said first and said second interactor domains to each other or simultaneously to a third polypeptide.

73. The DNA sequence according to Claim 72, wherein said marker protein is a β-lactamase.

74. A circularly permutated marker protein fused in frame through each of its N- and C- termini to a first interactor domain and a second interactor domain, wherein said circularly permutated marker protein functionally reassembles upon the binding of said first and said second interactor domains to each other or simultaneously to a third polypeptide.

75. The circularly permutated marker protein according to Claim 74, wherein said marker protein is a β-lactamase.

76. A method of high-throughput identification of compounds that inhibit phosphorylation-regulated cell signal transducers, said method comprising:

expressing from a plasmid in a host cell an oligopeptide comprised of in the direction of translation, a first interactor domain, a circularly permutated β-lactamase, and a second interactor domain, wherein said first interactor domain comprises a phosphorylation regulated cell signal transducer protein and said second interactor domain comprises an immunoglobulin variable region that binds to said first interactor domain only under the required state of phosphorylation, wherein the binding of said first interactor domain with said second interactor domain results in the functional reconstitution of said circularly permutated β-lactamase to produce a colored host cell in the presence of chromogenic β-lactamase substrate,

whereby production of a colored host cell is indicative of a compound that inhibits phosphorylation-regulated cell signal transduction.

77. The method according to Claim 76, wherein said phosphorylation-regulated cell signal transducer protein is a tyrosine kinase.

78. The method according to Claim 77, wherein said tyrosine kinase is Her-2/neu.

79. The method according to Claim 78, wherein said immunoglobulin variable region binds to Her-2/neu and said required state of phosphorylation is unphosphorylated.